Fatal Invasive Infection with Fungemia Due to *Microascus cirrosus* after Heart and Lung Transplantation in a Patient with Cystic Fibrosis[▽]

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***Scopulariopsis* species are rarely but increasingly recognized as opportunistic pathogens in immunocompromised patients. We report on a patient suffering from cystic fibrosis who developed disseminated fungal infection due to a rare *Scopulariopsis* species, *Microascus cirrosus*, after heart and lung transplantation. Despite antifungal combination therapy with voriconazole and caspofungin, the patient died 4 weeks after transplantation. Diagnostic difficulties and optimal management of disseminated *Scopulariopsis*/*Microascus* infections are discussed.**

CASE REPORT

A 36-year-old man suffering from cystic fibrosis was admitted to our hospital in June 2009 for a heart and bilateral lung transplantation. He had a first lung transplantation in 1997 but had chronic rejection since 2001 in spite of several immunosuppressive regimens. His medical history also included renal failure (hemodialysis since 2007), diabetes mellitus, and airway colonization with a multiresistant *Pseudomonas aeruginosa*. Short antifungal therapy courses had been prescribed over the past years for various yeasts (*Candida* spp.) and molds (*Aspergillus*, *Paecilomyces*, and *Fusarium* species) colonizing his respiratory tract, but there was no evidence of previous isolation of a *Scopulariopsis* species. At the time of admission, sputum cultures grew only *Candida albicans*, and fluconazole was thus prescribed (200 mg intravenously [i.v.] after each dialysis).

Following graft surgery, the immunosuppressive regimen included induction therapy with basiliximab (anti-CD25 antibody [20 mg i.v. on the day of transplantation and on day 4]) and solumedrol (10 mg/kg of body weight on the day of transplantation, followed by three 120-mg doses per day), followed by cyclosporine adjusted according to dialysis parameters to reach therapeutic blood levels (300 to 350 ng/ml) and solumedrol. Antimicrobial therapy consisted of a broad-spectrum antibiotherapy with tobramycin, vancomycin, piperacillin, and tazobactam. Although the patient seemed to do well in the early postoperative period, with apyrexia and extubation on day 3,

his white blood cell count (WBC) increased slowly starting on the day after transplantation, reaching 20×10^9 cells/liter by day 8 postsurgery. On day 11 after the operation (WBC = 30×10^9 cells/liter), a thoracic computed tomodensitometry (TDM) revealed bilateral pulmonary effusions (Fig. 1A), which were drained on day 19 without clinical improvement. Bilateral hemorrhagic pleural fluid specimens revealed several regular, hyaline, and branched septate hyphae on direct examination (Fig. 2A), leading to the diagnosis of proven invasive fungal infection (IFI) according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria (8). The patient was given an antifungal combination therapy of voriconazole i.v. (6 mg/kg every 12 h as a loading dose followed by two 4-mg/kg doses a day) and caspofungin (70 mg/day as a loading dose followed by 50 mg/day) while awaiting mycological identification. A bronchial fibroscopy, performed on day 23 because of subcutaneous emphysema and air bubbles coming from the pleural drain, highlighted pseudomembranes on the surgery scar. A thoracic TDM showed the persistence of the bilateral pleural effusions associated with pneumothorax and a slight pneumomediastinum (Fig. 1B). Surgery was decided on day 25 to suture the left pulmonary parenchyma and to remove pleural clots. A blood culture (Bactec Mycosis IC/F; Becton Dickinson, Sparks, MD) was positive on day 27. Direct smear examination revealed several filamentous and septate hyphae with intercalary chlamydospore-like cells (Fig. 2B). The patient died of multiorgan failure on day 28.

All serum *Aspergillus* galactomannan antigen assays (GM), performed over time on days 11, 14, 15, 24, and 25, were negative (Platelia *Aspergillus*; Bio-Rad, Marnes-la-Coquette, France). Fungal cultures of the bilateral pleural specimens

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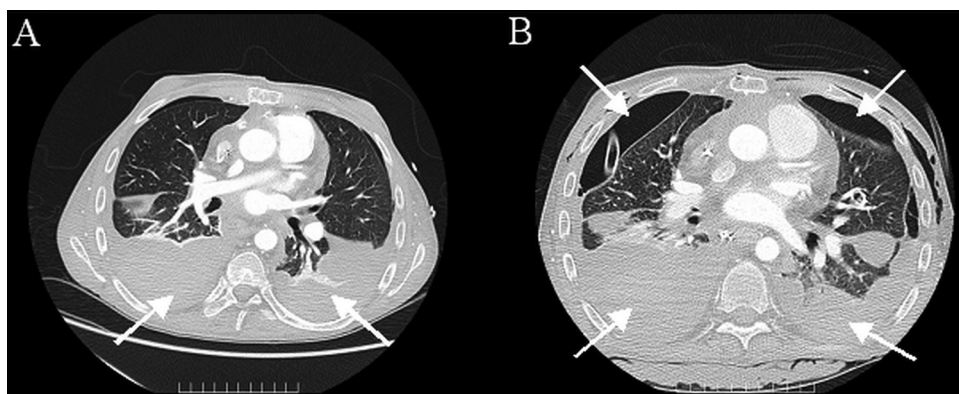▽ Published ahead of print on 4 May 2011.

FIG. 1. (A) Thoracic computed tomodensitometry (TDM) scan performed on day 11 after the operation revealing bilateral pulmonary effusions (white arrows). (B) TDM showing the persistence of bilateral pleural effusions (white arrows at the bottom of the scan) associated with a pneumothorax (white arrows at the top of the scan) on postoperative day 23.

withdrawn on day 19, and incubated at both 26°C and 35°C on Sabouraud's dextrose agar, revealed restricted, white and velvety colonies after 6 days of incubation. Microscopic examination revealed branched, hyaline, regular, and septate but sterile hyphae. All other specimens recovered on day 22 (bronchial secretions) and during surgery (intrapericardial fluid and a blood clot resulting from hemothorax and bronchial secretions) also revealed several septate hyphae after microscopic examination and Gomori-Grocott methenamine silver (GMS) stain and similar colonies after a few days of culture as well as for the blood culture. Identification was finally obtained after death, by sequencing the D1/D2 region of the 28S rDNA. Comparison of the nucleotide sequences (567 bp) with the GenBank database revealed 99.6% similarity with *Microascus cirrosus* reference strain CBS 217.31 (accession number AF275539) and 96% with *Scopulariopsis brevicaulis* strain IFM 54315 (accession number AB36375).

Several weeks later, phenotypic characteristics consistent with the genus *Scopulariopsis* were obtained using agar block culture on slides: annellidic and ampulliform conidiogenous cells produced chains of truncated, bullet-shaped, and smooth hyaline conidia, which became melanized in old cultures (Fig. 3). Unfortunately, and despite prolonged incubation for several months on different media (Sabouraud's dextrose agar, potato-dextrose agar [PDA], potato-carrot agar [PCA], and

oatmeal agar [OA]) and different temperatures (25°C and 30°C), no sexual stage (production of ascocarps, teleomorph) was obtained. Antifungal susceptibility testing was performed using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standardized methodology and Etest (21). Both techniques uncovered high MICs for all antifungal agents tested (8 μg/ml for amphotericin B, 4 μg/ml for caspofungin and terbinafine, and more than 8 μg/ml for itraconazole, voriconazole, and posaconazole).

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Although invasive aspergillosis (IA) remains, with candidiasis, the most frequent cause of invasive fungal infections (IFIs) worldwide, severe invasive infections due to other opportunistic hyphomycetes molds (including *Scedosporium*, *Fusarium*, and *Scopulariopsis*) are emerging in the ever-growing population of immunocompromised patients (32). In two recent multicenter prospective studies that investigated the incidence of IFIs in hematopoietic stem cell transplant (HSCT) recipients and solid-organ transplant (SOT) recipients, these molds accounted for up to 8% of all IFIs in both populations and up to 20% in lung transplant recipients (13, 19). Fungi belonging to the genus *Scopulariopsis* are widely found in our environment (soil, food, paper, and other substrates) (7). As a
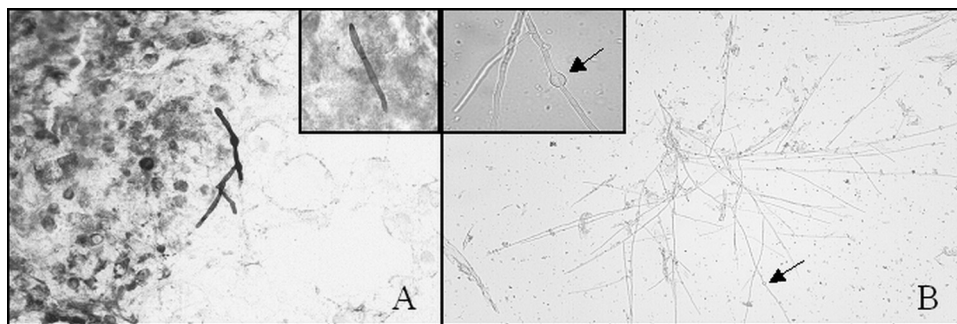

FIG. 2. (A) Direct microscopic examination of the pleural samples showing branched and septate hyphae (Gomori-Grocott staining, ×400 magnification). (B) Direct microscopic examination of the blood culture showing branched and septate hyphae (direct smear; ×100 magnification in the main image, ×1,000 magnification in the inset). The black arrows point to chlamydospore-like structures.
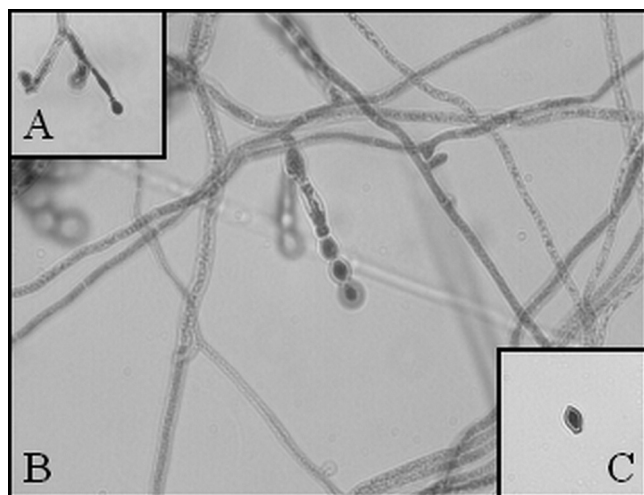
FIG. 3. Microscopic examination after lactophenol cotton-blue staining of the culture on Sabouraud's dextrose agar showing annellidic and ampulliform conidiogenous cells (A and B) along with truncated, bullet-shaped, smooth conidia (C) (×1,000 magnification).

result of its keratinolytic activity, superficial infections, such as onychomycosis in immunocompetent subjects (1 to 10% of such infections), are the most common clinical setting (4, 9). *Scopulariopsis* spp. have also been involved in a large spectrum of infections in immunocompromised subjects, including nasal infections, peritonitis, pulmonary infections, endocarditis as well as cerebral infections, and diagnosis is sometimes made at autopsy (2, 11, 12, 14, 18, 30, 31). Whereas *Scopulariopsis brevicaulis* accounts for most of the cases, other *Scopulariopsis* species, some existing as a sexual state or teleomorph (most in the genus *Microascus*), have also recently been described as human pathogens: *Scopulariopsis acremonium*, *S. brumptii*, *S. candida*, and *S. cinerea* (*Microascus cinereus*) (2, 3, 14, 20).

Herein, we report on a disseminated *M. cirrosus* infection after a heart and lung transplantation in a patient suffering from cystic fibrosis. In light of this case and previously reported cases, optimal management of these infections and diagnostic issues are discussed.

Disseminated infections (involving at least two noncontiguous sites and proved by histology and/or culture) due to *Scopulariopsis/Microascus* are uncommon (only eight cases have been reported since 1987). As shown in Table 1, most patients with disseminated infection were transplant recipients (five HSCT recipients or bone marrow transplant [BMT] recipients for hematological malignancy, and three SOT recipients, including two lung recipients). Dissemination to the skin seems to be a common event, being noted in more than half of the patients with disseminated *Scopulariopsis* infections (patients 2, 3, 4, 6, and 7 in Table 1). In the present case, infection occurred early (day 19) in the heart and bilateral-lung transplantation period in comparison to the case described by Wuyts et al., which involved a single-lung-transplant recipient (34). The hypothesis of possible transmission from the donor to our patient was excluded, as fungal cultures from the graft preservation fluid were negative. Such a difference in the median time to the onset of infection/diagnosis after solid-organ transplantation, according to the type of transplant, has been reported previ-

ously for IA (24). In this study, IA occurred earlier in the heart-lung transplant recipients (0.7 months) than in patients receiving bilateral (3.9 months) or single-lung transplants (5 months).

Disseminated *Scopulariopsis* infections are almost invariably fatal. Underlying conditions, delayed diagnosis, and a high level of resistance of *Scopulariopsis* to conventional antifungal agents are probably responsible for the poor outcome. MICs of amphotericin B, azoles, caspofungin, and terbinafine were high against our *M. cirrosus* isolate comparable to what is reported for clinical strains of *S. brevicaulis* (1, 5, 10). Potent synergistic activities between antifungal agents against *S. brevicaulis* have been reported with the highest synergistic effect for posaconazole and terbinafine (6). Other combinations, such as terbinafine with voriconazole or caspofungin with azoles (posaconazole and voriconazole), show synergy for some strains. Synergy of voriconazole with caspofungin was also obtained *in vitro* for a clinical isolate of *S. brevicaulis* recovered from a patient with disseminated infection (26). However, the patient died, as did our patient, when treated with the same antifungal combination, showing once again the lack of correlation between *in vitro* results and treatment efficacy.

The scarcity of *Scopulariopsis* infections explains the lack of consensus regarding the best antifungal regimen. Most patients (7/9) were prescribed various combination therapies with no obvious best regimen based on survival (Table 1). The contribution of surgery is also difficult to assess. Other compounds, such as miltefosine, widely used in the treatment of visceral leishmaniasis and exhibiting *in vitro* fungicidal activity against several molds, may need evaluation (29, 33). Adjuvant therapies with cytokines, such as gamma interferon, and growth factors, such as granulocyte colony-stimulating factor (G-CSF), have been used to treat IFIs, including *Scopulariopsis* infections (14, 25, 27, 30).

Difficulties encountered in the management of these disseminated infections underline the need for early diagnosis of these infections. As shown in Table 1, blood cultures may be important to diagnose invasive *Scopulariopsis* infections, as they are during infections by *Scedosporium* and *Fusarium* spp. Here, direct smear of the positive blood culture revealed several septate hyphae, some with an unusual aspect, harboring intercalary and ballooned, chlamydospore-like structures. This interesting and unusual feature has previously been described in *M. cirrosus* cultures, but to the best of our knowledge, it has never been reported in clinical samples (17). Antigen detection is potentially interesting. *Aspergillus* galactomannan was detected during a case of disseminated *S. brevicaulis* when there was no evidence of *Aspergillus* infection (22). Here, as in other cases of disseminated infection, all the GMs performed since the day of transplantation were negative. Although histopathological examination showing septate hyphae is an important step in diagnosis, species identification is mandatory and can require molecular methods, as in our case. Over the past 15 years, only two cases involving *M. cirrosus* (not included in our review because of focal infection or dissemination not proven) have been reported (15, 30).

The present case is the third description of invasive infection caused by *M. cirrosus* in humans and the first in a SOT recipient patient. It underlines the need for increased awareness of infections caused by uncommon molds in immunocompro-

TABLE 1. Clinical and mycological characteristics of previously published cases of disseminated *Scopulariopsis/Microascus* infection[a]

Patient	Age (yr)	Sex[b]	Type of transplant (if any) and underlying disease[c]	Time to diagnosis after transplantation	Mycological identification	Involved sites	Positive blood cultures	Antifungal agent(s)[d]	Surgery	Outcome (survival time after diagnosis)	Reference
1	17	M	BMT for CML	29 days	*Scopulariopsis* sp.	Nasal septum, trachea, lungs, brain	Yes	AMB	Yes	Death (26 days)	16
2	37	M	SOT (liver) for primary sclerosing cholangitis	3–4 mo	*S. brumptii*	Skin, brain, lungs	No	AMB-MIC	Yes	Death (6–7 wk)	20
3	41	F	No underlying disease		*S. brevicaulis*	Skin, lymph nodes, lungs	No	AMB-TRB, followed by TRB	Yes	Cure	23
4	10	M	HSCT (AML)	8–9 mo	*S. brevicaulis*	Skin, heart, lungs, kidneys, thorax	Yes	VRC-CAS	No	Death (11 days)	26
5	63	M	SOT (lungs) for chronic obstructive pulmonary disease	7–8 mo	*S. acremonium*	Heart, thyroid gland, stomach, kidneys, lungs	No	VRC-CAS	No	Death (1 day)	34
6	38	F	HSCT for AML	190 days	*S. brevicaulis*	Skin, lungs	No	AMBL, followed by AMBL-CAS, followed by AMBL-VRC	No	Death (22 days)	22
7	56	M	HSCT for CML	5–6 mo	*Scopulariopsis* sp.	Skin, lungs	No	AMBL-POS	No	Death (20 days)	28
8	50	F	HSCT for MM	499 days	*S. acremonium*	Sinus, vessel walls of carotid artery and middle cerebral artery	No	AMBL, followed by CAS	No	Death[e]	3
9	36	M	SOT (heart and lung) for cystic fibrosis	19 days	*M. cirrosus*	Pleural fluid, intrapericardial fluid, blood clots, bronchial secretions	Yes	VRC-CAS	No	Death (9 days)	Present case

[a] Only cases involving at least two noncontiguous sites proved by histology and/or culture were considered.
[b] M, male; F, female.
[c] Abbreviations: BMT, bone marrow transplant; CML, chronic myelogenous leukemia; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; MM, multiple myeloma.
[d] Antifungal agent abbreviations: AMB, amphotericin B; AMBL, liposomal amphotericin B; CAS, caspofungin; ITC, itraconazole; MIC, miconazole; POS, posaconazole; VRC, voriconazole; TRB, terbinafine.
[e] Death occurred early in the days following the diagnosis.

mised patients. Finally, in light of this and previously reported cases, several questions are raised. (i) Which antifungal(s) should be administered? (ii) Is there a place for adjuvant therapy, such as immunomodulatory regimens or new agents such as miltefosine, in the management of these highly life-threatening infections? Larger case series or prospective studies will probably help answer these questions and allow us to establish guidelines for the management of invasive *Scopulariopsis*/*Microascus* infections in immunocompromised patients.

Nucleotide sequence accession numbers. The nucleotide sequence of the isolate has been deposited in GenBank database under accession number HQ676488.

REFERENCES

1. **Aguilar, C., I. Pujol, and J. Guarro.** 1999. *In vitro* antifungal susceptibilities of *Scopulariopsis* isolates. Antimicrob. Agents Chemother. **43:**1520–1522.
2. **Baddley, J. W., S. A. Moser, D. A. Sutton, and P. G. Pappas.** 2000. *Microascus cinereus* (anamorph *Scopulariopsis*) brain abscess in a bone marrow transplant recipient. J. Clin. Microbiol. **38:**395–397.
3. **Beltrame, A., et al.** 2009. A fatal case of invasive fungal sinusitis by *Scopulariopsis acremonium* in a bone marrow transplant recipient. Int. J. Infect. Dis. **13:**e488–e492.
4. **Bonifaz, A., P. Cruz-Aguilar, and R. M. Ponce.** 2007. Onychomycosis by molds. Report of 78 cases. Eur. J. Dermatol. **17:**70–72.
5. **Cuenca-Estrella, M., et al.** 2003. *Scopulariopsis brevicaulis*, a fungal pathogen resistant to broad-spectrum antifungal agents. Antimicrob. Agents Chemother. **47:**2339–2341.
6. **Cuenca-Estrella, M., et al.** 2006. *In vitro* activities of 10 combinations of antifungal agents against the multiresistant pathogen *Scopulariopsis brevicaulis*. Antimicrob. Agents Chemother. **50:**2248–2250.
7. **De Hoog, G. S., J. Guarro, J. Gene, and M. J. Figueras.** 2000. Atlas of clinical fungi, 2nd ed. Centraalbureau voor Schimmelcultures, Utrecht, the Netherlands.
8. **De Pauw, B., et al.** 2008. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. **46:**1813–1821.
9. **Filipello Marchisio, V., A. Fusconi, and F. L. Querio.** 2000. *Scopulariopsis brevicaulis*: a keratinophilic or a keratinolytic fungus? Mycoses **43:**281–292.
10. **Garcia-Effron, G., et al.** 2004. *In vitro* activity of terbinafine against medically important non-dermatophyte species of filamentous fungi. J. Antimicrob. Chemother. **53:**1086–1089.
11. **Hart, A. P., D. A. Sutton, P. J. McFeeley, and M. Kornfeld.** 2001. Cerebral phaeohyphomycosis caused by a dematiaceous *Scopulariopsis* species. Clin. Neuropathol. **20:**224–228.
12. **Isidro, A. M., et al.** 2006. Fungal prosthetic mitral valve endocarditis caused by *Scopulariopsis* species: case report and review of the literature. J. Thorac. Cardiovasc. Surg. **131:**1181–1183.
13. **Kontoyiannis, D. P., et al.** 2010. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin. Infect. Dis. **50:**1091–1100.
14. **Kriesel, J. D., E. E. Adderson, W. M. Gooch III, and A. T. Pavia.** 1994. Invasive sinonasal disease due to *Scopulariopsis candida*: case report and review of scopulariopsosis. Clin. Infect. Dis. **19:**317–319.
15. **Krisher, K. K., N. B. Holdridge, M. M. Mustafa, M. G. Rinaldi, and D. A. McGough.** 1995. Disseminated *Microascus cirrosus* infection in pediatric bone marrow transplant recipients. J. Clin. Microbiol. **33:**735–737.
16. **Neglia, J. P., D. D. Hurd, P. Ferrieri, and D. C. Snover.** 1987. Invasive *Scopulariopsis* in the immunocompromised host. Am. J. Med. **83:**1163–1166.
17. **Nishimura, K., and M. Miyaji.** 1985. Dimorphism of *Microascus cirrosus*. Mycopathologia **90:**29–33.
18. **Nwabuisi, C., A. K. Salami, N. A. Abdullahi, and O. O. Agbede.** 2003. *Scopulariopsis* associated meningitis in adult Nigerian AIDS patient—a case report. West. Afr. J. Med. **22:**364–365.
19. **Pappas, P. G., et al.** 2010. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin. Infect. Dis. **50:**1101–1111.
20. **Patel, R., et al.** 1994. Phaeohyphomycosis due to *Scopulariopsis brumptii* in a liver transplant recipient. Clin. Infect. Dis. **19:**198–200.
21. **Rodriguez-Tudela, J. L., et al.** 2008. EUCAST Technical Note on the method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for conidia-forming moulds. Clin. Microbiol. Infect. **14:**982–984.
22. **Salmon, A., et al.** 2010. Disseminated *Scopulariopsis brevicaulis* infection in an allogeneic stem cell recipient: case report and review of the literature. Clin. Microbiol. Infect. **16:**508–512.
23. **Sellami, A., et al.** 2003. Infection disséminée à *Scopulariopsis brevicaulis*. J. Mycol. Med. **13:**203–206.
24. **Singh, N., and S. Husain.** 2003. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. J. Heart Lung Transplant. **22:**258–266.
25. **Steinbach, W. J., and D. A. Stevens.** 2003. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. Clin. Infect. Dis. **37:**S157–S187.
26. **Steinbach, W. J., W. A. Schell, J. L. Miller, J. R. Perfect, and P. L. Martin.** 2004. Fatal *Scopulariopsis brevicaulis* infection in a paediatric stem-cell transplant patient treated with voriconazole and caspofungin and a review of *Scopulariopsis* infections in immunocompromised patients. J. Infect. **48:**112–116.
27. **Stevens, D. A., E. Brummer, and K. V. Clemons.** 2006. Interferon-gamma as an antifungal. J. Infect. Dis. **194:**S33–S37.
28. **Swick, B. L., S. C. Reddy, A. Friedrichs, and M. S. Stone.** 2010. Disseminated *Scopulariopsis*—culture is required to distinguish from other disseminated mould infections. J. Cutan. Pathol. **37:**687–691.
29. **Tong, Z., et al.** 2007. In vitro activities of miltefosine and two novel antifungal biscationic salts against a panel of 77 dermatophytes. Antimicrob. Agents Chemother. **51:**2219–2222.
30. **Ustun, C., G. Huls, M. Stewart, and K. A. Marr.** 2006. Resistant *Microascus cirrosus* pneumonia can be treated with a combination of surgery, multiple anti-fungal agents and a growth factor. Mycopathologia **162:**299–302.
31. **Vaidya, P. S., and J. F. Levine.** 1992. *Scopulariopsis* peritonitis in a patient undergoing continuous ambulatory peritoneal dialysis. Perit. Dial. Int. **12:**78–79.
32. **Walsh, T. J., et al.** 2004. Infections due to emerging and uncommon medically important fungal pathogens. Clin. Microbiol. Infect. **10:**48–66.
33. **Widmer, F., et al.** 2006. Hexadecylphosphocholine (miltefosine) has broad-spectrum fungicidal activity and is efficacious in a mouse model of cryptococcosis. Antimicrob. Agents Chemother. **50:**414–421.
34. **Wuyts, W. A., et al.** 2005. Fatal *Scopulariopsis* infection in a lung transplant recipient: a case report. J. Heart Lung Transplant. **24:**2301–2304.